REMARKS

In the Final Office Action, the Examiner maintained two rejections, namely the rejection of Claims 1-13 under 35 U.S.C. §112, first paragraph as being allegedly non-enabling; and rejection of Claims 1-13 under 35 U.S.C. §103, as being unpatentable over Nagata *et al.,* and Yoshimura *et al.* Claims 14-17 of the originally filed application (U.S. Patent Application Serial No. 08/608,568) have been passed to allowance. Applicants file the present application in order to prosecute Claims 1-13 of the originally filed application (U.S. Patent Application Serial No. 08/608,568).

1) Claims 1-13 are Enabled, and Patentable Under 35 U.S.C. §112, First Paragraph

In the Final Office Action, the Examiner rejected Claims 1-13 under 35 U.S.C. §112, first paragraph as being allegedly non-enabling. Applicants must respectfully disagree. The Examiner maintains that the present "specification fails to provide specific guidance for a person skilled in the art to practice the instant invention without undue experimentation. The phrase 'serine threonine inhibitor' is broad and by referring to most common pharmaceutical textbooks a person skilled in the art will not be able to arrive at the list of the compounds encompassed under such phrase" (Final Office Action, p. 2).

First, "[t]he key word is 'undue' not 'experimentation.'" *In re Angstadt and Griffin,* 190 USPQ 214, 219 (CCPA 1976). "[A] considerable amount of experimentation is permissible . . . if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed . . . ." *Ex parte Jackson,* 217 USPQ 804, 807 (Bd. App. 1982); *In re Wands,* 8 USPQ 2d 1400, 1404 (CAFC 1988). The Examiner must not lose sight of the fact that experimentation is permissible, even considerable experimentation, "if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Ex parte Forman,* 230 USPQ 546, 547 (Bd. Pat. App. & Int'f. 1986). Applicants assert that the person of ordinary skill in the art is likely only to use the "common pharmaceutical textbook" as merely a starting point. In order to determine if a particular serine threonine kinase inhibitor is encompassed by the present Claims, the

compound must meet the functional definition of serine-threonine kinase inhibitors, not a structural definition.

Applicants believe that more than sufficient guidance is provided in the Description of the Invention and the Examples to teach one of ordinary skill in the art to identify and use serine threonine kinase inhibitors that are useful in enhancing aqueous humor outflow. Applicants also believe that the factors set forth in *Ex parte Forman* (*Ex parte Forman*, 230 USPQ 546 [1](Bd. Pat. App. & Int'f. 1986)) are met in the present application. For example, Applicants strenuously contend that the application sets forth detailed protocols for screening any serine-threonine kinase inhibitor useful for enhancing aqueous humor outflow. This is reflected in the explicit definition of "serine-threonine kinase inhibitor" in our application (*See,* page 9, lines 1-7; and the detailed discussion of this class of compounds on page 26 line 25, through page 29, line 20).

In specific, the Examples of the present application provide more than sufficient guidance as to the selection of suitable compounds. For instance, the specification states "as described in detail in the Experimental section, these screening procedures have been employed in the experiments performed on compound H-7" (p. 25, lines 11-13). As indicated in Table 2A (p. 24), the screening procedure to initially evaluate serine-threonine kinases include the following steps: I) Examination of the *in vitro* the effect of compounds on corneal endothelial cells (*e.g.*, monkey, cat, rabbit) and morphology in culture; II) Determine the effect of compounds on overall ocular tolerability/toxicity; and III) Determine the effect of compounds administered topically on the intraocular pressure by non-invasive measurement techniques (*e.g.*, applanation tonometry). Compounds that show promise can then be examined in a more comprehensive screening procedure, as indicated in Table 2B (p. 25). As indicated in Table 2B, the follow-up screening method includes: I) Determine compounds effectiveness on outflow facility in living monkeys; II) Document whether compound is acting directly on the trabecular meshwork in living monkeys with disinserted ciliary muscle; III) Perform electron microscopy to analyze the effect of the compounds on the structure of the

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[1] The "Forman factors" used in making the determination of whether undue experimentation is necessary are set forth on page 547 of *Ex parte Forman.* These factors are: quantity of experimentation necessary; the amount of direction or guidance presented; the presence or absence of working examples; the nature of the invention; the state of the prior art; the relative skill of those in the art; the predictability or unpredictability of the art; and the breadth of the claims.

trabecular meshwork and other tissues; IV) Determine compounds effect on other properties, including refraction, accommodative and pupillary responses to pilocarpine; and corneal endothelial cell counts and morphology; and V) Consider clinical trials on human subjects.

As indicated in the Specification (*See e.g.,* p. 22), the screening (evaluation) procedures described hereafter can be used to test compounds that might exhibit beneficial effects by altering the cytoskeleton or the cell-cell or cell-extracellular matrix adherens junctions. Specifically, it can be used to examine compounds that might affect cell junctions through perturbation of actin filament integrity or membrane anchorage or inhibition of contractility. Those compounds which affect junction integrity or the integrity of the microfilament system are selected for further analysis. The effective concentrations in culture also serve as guidelines for the live animal experiments.

The same screening procedures were utilized by Dr. Kaufman to identify other compounds with desirable activities (Kaufman Decl., ¶¶7-9). As the Examiner has provided no evidence or explanation for doubting the truth or accuracy of any the statements in the present application, the Applicants' specification must be presumed to fulfill the enablement requirement of 35 U.S.C. §112, first paragraph. Indeed, Drs. Kaufman and Geiger's claims are directed to kinase inhibitors that affect aqueous humor outflow (*e.g.,* H-7, ML-7, staurosporine, and KT-5926)(*See e.g.,* Kaufman Decl., ¶10). In specific, their work on H-7, ML-7, and staurosporine, shows that these compounds dramatically affect cell contractility and increase aqueous humor outflow facility via their junction and cytoskeleton-disrupting activities.

Applicants therefore respectfully request that this rejection be withdrawn.

2) CLAIMS 1-13 ARE UNOBVIOUS OVER NAGATA *ET AL.* AND YOSHIMURA *ET AL.*

The Examiner has also maintained the rejection of Claims 1-13 under 35 U.S.C. §103, as being unpatentable over Nagata *et al.* and Yoshimura *et al.* Applicants must continue to respectfully disagree. Applicants contend that the Examiner has not presented a *prima facie* case of obviousness, as the teachings of Nagata *et al.* and Yoshimura *et al.* would not suggest the claimed invention to one of ordinary skill in the art with an understanding of these

references. Furthermore, the Examiner's assumptions do not constitute the disclosure of the prior art (*In re Rijckaert*, 9 F.3d. 1531 (Fed. Cir., 1993)).

As indicated in the accompanying Declaration of Dr. Mittag, a co-author of the Yoshimura *et al.* paper, this reference describes work conducted in Dr. Mittag's laboratory (Mittag Decl., ¶5). Indeed, Dr. Mittag wrote most of the paper, and supervised its production (Mittag Decl., ¶5). This reference describes some of the mechanism(s) involved in regulating the **formation** of aqueous humor by the ciliary processes of the eye. Specifically, this paper characterizes one of the biochemical steps that connects receptor signals to the fluid transport systems of the ciliary process tissue, namely kinase enzyme activity.

As described in Dr. Mittag's Declaration (Mittag Decl., ¶9), there are anatomic and physiologic distinctions between the ciliary epithelium and the trabecular meshwork. The ciliary epithelium governs aqueous humor inflow (*i.e.,* formation) by active secretion, while the trabecular meshwork governs aqueous humor outflow by passive bulk fluid drainage. In addition, ion transport is involved in the formation of aqueous humor by a geometrically unaltered secretory epithelium (*i.e.,* ciliary epithelium), while cytoskeletal attenuation, cell junction weakening, and cell separation result in the passive drainage of bulk fluid through a geometrically altered resistive pathway (*i.e.,* trabecular meshwork). Thus, the physiologic and anatomic systems associated with enhancing aqueous humor outflow (*i.e.,* the subject of the present claims), and the formation of aqueous humor (*i.e.,* the Yoshimura and Nagata references) are very different, and distinct each from the other (*See e.g.*, Mittag Decl., ¶¶6-7).

Dr. Mittag confirms that he did not report on the tissue responsible for the *outflow* of aqueous humor, namely the trabecular tissue, nor did he characterize the kinase activities in trabecular tissue (Mittag Decl., ¶8). Furthermore, his use of the compound H-7 was entirely for the purpose of differentiating various kinase activities in ciliary process tissue on a biochemical basis (*i.e.,* the relative degree of inhibition of aqueous humor formation by H-7). He did not conduct experiments with H-7 to determine the cellular responses of eye tissue to this agent (*e.g.,* cytoskeleton changes), nor did he do any experiments to determine the effects of H-7 on aqueous humor dynamics in the intact eye (Mittag Decl., ¶8).

As discussed by Dr. Kaufman (Kaufman Decl., ¶12), Nagata *et al.* address the involvement of protein kinase C (PKC) in the regulation of ion transport and consequent aqueous humor formation. There is no mention in Nagata *et al.* of enhancement of aqueous

humor outflow from the anterior chamber via the trabecular meshwork, or of cell junctions, or cytoskeletal proteins. Indeed, like the Yoshimura *et al.* reference, there is no discussion **at all** in Nagata *et al.* of outflow of aqueous humor. Rather, Nagata *et al.* discuss experiments conducted on ciliary epithelia, namely tissue that is involved in aqueous humor formation. Thus, Nagata *et al.* is similar to the Yoshimura *et al.* paper, in that these authors report work conducted on aqueous humor formation, not outflow (Kaufman Decl., ¶¶12-13). Furthermore, the cytoskeletal action and non-PKC pathway underlying the effects on the trabecular meshwork and aqueous outflow were not even known at the time of the Yoshimura *et al.* and Nagata *et al.* publications, thus these references could not suggest to one of skill in the art to use serine threonine kinase inhibitors to increase aqueous humor outflow. Thus, contrary to the law, the Examiner has imbued one of ordinary skill in the art with knowledge of the invention, when no prior art reference or references of record convey or suggest that knowledge, thus falling victim to the insidious effect of a hindsight syndrome (*W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983)).

Furthermore, it is impermissible to first ascertain factually what the present Applicants *did* and then view the prior art in such a manner as to select from the random facts of that art only those which may be modified and then utilized to reconstruct Applicants' invention from such prior art (*Interconnect Planning Corp. v. Feil*, 227 USPQ 543, 551, 774 F.2d 1132, 1143 (Fed. Cir. 1985), quoting *In re Shuman*, 361 F.2d 1008, 1012, 150 USPQ 54, 57 (CCPA 1966)). "Not only must the claimed invention as a whole be evaluated, but so also must the references, as a whole, so that their teachings are applied in the context of their significance to a technician at the time -- a technician **without our knowledge of the solution**." (emphasis added). Applicants contend that this would have been impossible in the present case, as these references could not suggest to one of skill in the art to use serine threonine kinase inhibitors to increase aqueous humor outflow.

In contrast to the Nagata *et al.* abstract and Yoshimura *et al.* paper, the present patent application is directed to methods for the enhancement of aqueous humor outflow from the anterior chamber via the trabecular meshwork, by modulation of cytoskeletal proteins and cell junctions (Kaufman Decl., ¶13). It is Dr. Mittag's opinion as one of skill in the art, that the Examiner has misinterpreted the work described in his paper and by Nagata *et al.*, as neither

publication "teach[es] the effect of the claimed [compound] on the enablement of aqueous humor outflow and regulation of intra-ocular pressure." (Mittag Decl., ¶10).

In addition, in contrast to Nagata *et al.* and Yoshimura *et al.*, the present invention relates exclusively to enhancing aqueous humor outflow (*i.e.,* from the anterior chamber via the trabecular meshwork by modulation of cytoskeletal proteins and cell junctions). The present invention does not involve any effects on ion transport, aqueous humor formation, or other biological processes in the ciliary epithelium of the posterior chamber. Indeed, as indicated by Dr. Kaufman (Kaufman Decl., ¶¶13-14, and Tab 4), there are data showing that H-7 has **no effect** on aqueous humor formation in the live monkey (Kaufman Decl., ¶13). Furthermore, the H-7 effect on the cytoskeleton and cell junctions does not involve the protein kinase C pathway (*See,* Kaufman Decl., ¶13).

Further in contrast to Nagata *et al.*, who describe the involvement of protein kinase C (PKC) in regulating intraocular pressure, the present invention does not teach any involvement of PKC in the effect of inhibitors (*e.g.,* H-7) on the actin cytoskeleton, cell adhesion, or outflow facility. Indeed, Drs. Kaufman and Geiger have evidence that specific PKC inhibitors have no such an effect on the actin cytoskeleton, cell adhesion or *outflow* facility (*See,* Kaufman Decl., ¶15, and Volberg *et al.* attached at Tab 6 to the Kaufman Declaration). Finally, Yoshimura *et al.* report studies on protein kinase activity in rabbit ciliary processes (*i.e.,* structures involved in aqueous humor formation). In contrast, all of Dr. Kaufman and Geiger's measurements relate to the trabecular meshwork/Schlemm's canal (*i.e.,* structures involved in aqueous humor outflow), and not to the ciliary process (*i.e.,* structures involved in aqueous humor formation or inflow)(*See*, Kaufman Decl., ¶16). Therefore, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that Applicant's claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect at (650) 299-8120.

Respectfully submitted,
MEDLEN & CARROLL,LLP

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Kamrin T. MacKnight
Registration No. 38,230

MEDLEN & CARROLL, LLP
220 Montgomery Street, Suite 2200
San Francisco, California 94104
415/705-8410